UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/480,389	01/11/00	BOMAN	B CATX-N

024988
LEONA L LAUDER
369 PINE STREET
SUITE 610
SAN FRANCISCO CA 94104-3313

HM22/1106

EXAMINER	
HOLLERAN, A	
ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/480,389	Applicant(s) BOMAN, BRUCE M.
	Examiner Anne Holleran	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28,31-44 and 54-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28,31-44 and 54-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,6,8,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II in Paper No. 13, filed August 20, 2001, is acknowledged. Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement between the inventions of Group I and Group II. The election of Group II has been treated as an election without traverse (MPEP § 818.03(a)). Applicant traversed the election of species requirement on the basis that the species are presented in claims reciting species are Markush claims and that the courts have stated that in many cases Markush claims do not include inventions that would otherwise be considered independent. This argument is not found persuasive because, in the instant case, the different species presented in the claims is independent because each species is a separate and distinct gene that encodes a separate and distinct protein. Thus, a separate search is required for each species.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-6, 9-23, and 45-53 are canceled by the amendment filed August 20 2001.

Claims 7, 8, 29 and 30 were canceled by the amendment filed April 26, 2001.

Claims 55-60 are added.

Claims 24-28, 31-44 and 54-60 are pending and examined on the merits to the extent the methods read on methods of quantifying MLH1 and MSH2 proteins.

Claim Rejections - 35 USC § 112

3. Claims 24-28, 31-44 and 54-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is indefinite because of the recitation of the phrase "normal biological sample". The scope of "normal biological sample" is not defined in the specification.

Claim 25 is indefinite because the phrase "the comparable mean or means of ratios" lacks antecedent basis in claim 24.

Claim 25 is indefinite because it is not clear what is mean by the last phrase "that are unaffected by said disease or by said disease susceptibility trait". It is not clear if this phrase is modifying the biological samples. Furthermore, because the claimed methods are drawn to methods for detecting germline mutations, the specification teaches that all biological samples will be affected by the disease susceptibility trait, i.e. all biological samples should have altered levels of protein expression.

4. Claims 24-28, 31-41, 43, 44 and 54-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods where the subject genes are MLH1 and MSH2, does not reasonably provide enablement for practicing the claimed methods with any subject genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claimed methods are drawn to methods of detecting a disease or disease susceptibility trait in an organism, where the disease or disease susceptibility trait is associated with a germline mutation in one of two or more subject genes, comprising quantifying immunologically the amount of wild-type protein expressed by the subject genes; calculating a ratio of the amount of the wild type protein of one of the subject genes to each of the other subject genes; and determining whether the ratio reflects an abnormally low level of wild-type protein expressed by any of the subject genes. The specification provides an example with predicted ratio outcomes of a Western blot immunoassay, where the predicted ratio outcomes are based on the assumptions that a mutation in one gene will result in a decrease in expressed protein for that gene, and that all organisms will only have one mutation in one of the genes. No ratio is predicted if an organism happens to have mutations in both of the subject genes. The predicted ratio example is limited to an immunoassay of MLH1 and MSH2, and the organism is a human.

The claims are broadly drawn to detection of any disease or disease susceptibility, in any organism or any subject gene. However, the specification confines its examples to cancer, in the human organism and to the subject genes of MLH1 and MSH2. Because of the breadth of the

claims and the limited teachings of the specification it is not clear that breadth of the claims is fully supported by the specification. If the art were predictable and the teachings of the specification could readily be extrapolated to the any organism, any subject gene and any type of disease, then the breadth of the claims would not be a factor in considering enablement. However, the art of genetic mutation and its relationship to disease or disease susceptibility does not appear to be predictable. Many cancers are associated with genetic mutations, but not all mutations result in a decreased expression of the protein. In the case of p53, one common mutation results in a protein product that is more stable than the wild-type protein, so that if a protein detection assay is used to detect p53, an increased amount of protein would be detected (Passlick et al, The Journal of Thoracic and Cardiovascular Surgery, 109(6): 1205-1211, 1995; see page 1205-1206). Furthermore, it appears that detection of protein immunologically does not correlate with detecting functional protein. Thus, it appears that before one of skill in the art may practice the full scope of the claimed invention, one would have to engage in further, undue experimentation, to establish that a correlation existed between a given disease or disease susceptibility and a decrease in protein expression levels.

In view of the lack of correlation between the scope of the claims and the scope of the teachings in the specification and further in view of the unpredictability of using protein quantification techniques as a measure of genetic mutation and loss of functional protein, one of skill in the art would have to engage in undue experimentation to make and use the claimed invention for the detection of any disease or any disease susceptibility trait in any organism comprising the detection of any subject gene, where the disease or disease susceptibility was associated with a decrease in a the level of the expressed protein relative to a second protein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 24-28, 31-43 and 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vogelstein et al (WO 97/08341; published 6 March 1997).

Vogelstein teaches a method for the detection of diseases associated with germline mutations. The genes may be MlH1 and MSH2 (page 4, lines 1-2). The method comprises detection of protein expression by Western blot (page 10 –page 11). Vogelstein teaches that a decrease in protein expression is associated with a mutation causing the disease and specifically uses the example of measuring MSH2 levels. The biological sample is peripheral blood lymphocytes, derived from a body fluid, blood. The method is diagnostic or prognostic of cancer. MSH2 is a mismatch repair gene. The organism is human, a mammal and a vertebrate. Vogelstein fails to teach a method comprising calculating a ratio of the amount of one of the subject genes to another subject gene. However, it would have been prima facie obvious to one of skill in the art at the time the invention was made to have calculated a ratio between one of the subject genes of Vogelstein and any other protein that one may have decided was a subject gene for the purpose of quantifying the Western blot results. Vogelstein shows that a decrease in MSH2 protein levels is associated with FAP. To quantify this decrease, would only require

comparing the level to a second protein that one assumed would not change in amount due to FAP.

6. Claims 24 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vogelstein et al (WO 97/08341; published 6 March 1997) in view of Kinzler et al (U.S. Patent 6,048,701; issued April 11, 2000; effective filing date June 7, 1995).

Claim 44 is drawn to methods were the protein detection is automated. Vogelstein teaches as described above, but fails to teach automated immunological methods. However, automated immunological methods are well known in the art as evidenced by the teachings of Kinzler. Kinzler teaches that immunological methods of detecting proteins of genes such as MSH2 are known in the art, methods such as fluorescence activating cell sorting (see col. 4, lines 47-52). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of Vogelstein by automating the immunological methods of detecting MSH2 protein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
November 5, 2001

[illegible]